the compositions of the invention to correct estrogen deficiencies.

The Office action further alleges that the specification provides no guidance of how correcting estrogen deficiencies would work.

Quite to the contrary, the present specification provides detailed information on administration of the disclosed compositions in estrogen replacement therapy and indeed Claim 18 itself specifically recites oral administration of a specific composition in a specific manner.

Withdrawal of this rejection is requested.

Claims 19 through 26 and 30 have been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement.

The Office action alleges that there is no support for "preventing osteoporosis" in the disclosure and that this is also considered new matter. Once again, Applicants point out that the use of the compositions of the invention to prevent osteoporosis is clearly disclosed in the specification as filed. In fact, the specification at page 4, penultimate paragraph, states "[a] further object of this invention is the use of the compositions according to the invention to correct estrogen deficiencies and to prevent osteoporosis and cardiovascular disorders in menopausal women."

The Office action alleges that the disclosure should contain representative examples which provide reasonable assurance to ones skilled in the art that a composition which falls within the scope of the claims will possess the alleged activity, and that the invention as claimed cannot be predicted but must be determined from the case to case by painstaking experimental study. "When the above factors are weighed together, one of ordinary skill in the art will be burdened with undue 'painstaking experimental study' to

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determine the compositions as claimed for all the estrogen, progestin and folic acid combinations."

Applicants point out that the invention as claimed is not directed to broad combinations of estrogen, progestin and folic acid. The invention as claimed is directed to the use of a limited class of compounds, where the estrogenic compound is not "an estrogen" but rather free estradiol or an estradiol ester, particularly estradiol valerate, and that the progestin is not a generic progestin but rather is nomegestrol acetate. None of the rejected claims mentions folic acid.

Thus, no "painstaking experimental study" is necessary to determine which compounds are effective; the claims are limited to the effective compounds and the effective dosages. Contrary to the allegation made in paragraph 6 of the Office action, only a limited class of compounds is claimed and the use of such compounds is supported by experimental study reported in the present specification.

Withdrawal of this rejection is requested.

Claims 3, 4, 7, 8, 13, 18 through 21, 25, 26, 30 and 31 have been rejected under 35 USC 103(a) over Plunkett et al and Blanc et al. Plunkett et al is directed to a method of hormonally treating menopausal disorders in women, by administering estrogen continuously for a period of time or continuously, in combination with a progestin. While estradiols and their esters are disclosed, the only examples are directed to cyclic administration of estrogens, and nomegestrol is not disclosed at all.

Blanc et al discloses continuous hormone replacement therapy for menopause comprising an oral dose of nomegestrol acetate, and either percutaneous, transdermal or oral estradiol. The nomegestrol acetate is administered in a higher amount than that which is presently claimed.

Applicants now submit a declaration of inventor Jacques

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Paris which addresses this rejection. The inventor points out that nomegestrol acetate is not comparable to other progestins, and has an original pharmacological profile which is not shared with any other available progestin. Contrary to 19-nortestosterone derivatives, it does not have any androgenic and estrogenic residual activity, and contrary to 17 α-hydroxyprogesterone derivatives, it has strong antigonadotropic activity. Thus, there is no equivalence between nomogestrol acetate and other progestins and one cannot predict what the effect of any particular dosage will be.

The declaration further points out that according to Blanc et al, the amenorrhea rate was 60% when oral nomegestrol acetate was combined with oral estradiol valerate, as compared with 78% when oral nomegestrol acetate was combined with percutaneous estradiol. There is no suggestion whatever in Blanc et al to lower the dosage of nomegestrol acetate with a view toward correcting estrogen deficiencies or preventing osteoporosis, and then select a regimen where both nomegestrol acetate and estrogen are administered orally in the claimed ranges. In fact, Blanc et al teaches that the rate of amenorrhea achieved with a continuous combined HRT for menopause is an important factor in patient compliance and based on the Blanc et al data, those of ordinary skill in the art seeking to improve the rate of amenorrhea and hence patient compliance would have been deterred from using an oral estrogen in combination with oral nomegestrol acetate.

Table 2 on page 24 of the present specification shows the results of biopsies of the endometria of women treated with a combination of the invention and a comparison is made with a combination containing the combination of Blanc et al. It can be seen from this data that the number of atrophic endometria significantly increased at the dosages of 1.25 mg and 0.625 mg

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of nomegestrol acetate, as compared to the dosage of 2.5 mg taught by Blanc et al. This result shows that the endometrium is protected because when the endometrium is atrophic, no hyperplasia occurs. At the same time, the low dosages of nomegestrol acetate are insufficient to induce a secretory transformation of the endometrium, as can be seen from Table 2. Thus, it is surprising and unexpected that dosages which are insufficient to induce a secretory transformation of the endometrium, when administered with an estrogen nevertheless exerts a protecting effect on the endometrium by keeping it in an atrophic state.

Two examples are reported in the declaration regarding administration of the composition of the invention for correcting estrogenic deficiencies and preventing osteoporosis. The results reported show that the combination of the invention was able to decrease bone resorption and prevent osteoporosis.

Accordingly, Applicants have shown that the combination of the invention provides unique and unexpected effects, which could not be predicted based on the disclosures of Plunkett et al and Blanc et al, and which do not in combination suggest continuous administration of estradiol or an ester thereof, and nomegestrol acetate in the claimed amounts.

Withdrawal of this rejection is requested.

In view of the foregoing remarks, Applicants submit that the present application is now in condition for allowance and an early allowance of the application is earnestly solicited.

Respectfully submitted,

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